

## Independent evidence-based health care

What interesting questions *Bandolier* readers ask. This month the whole issue is taken with finding answers (of a sort, perhaps) to questions we have been asked over the last few months. For most there is some evidence, though the more perceptive will have guessed that where there is no evidence (nada, zero, none) we duck the answers.

*Bandolier* was recently called eclectic in its choice of subjects. Well, maybe, but much of that eclecticism reflects the real need for information that you, the readers and users of evidence, have. Your demand for information illuminates our ignorance, and though the light may be dim at first, we soon want to turn up the watts and find out more. So keep the questions coming.

One question for which *Bandolier* has found a hint of an answer is the old chestnut about compliance and the number of times a day we have to take the tablets. A solid, if ageing, review confirms that. But it raises lots of other questions, and the *Bandolier* view is that there are a few theses begging to be written by aspiring pharmacists.

It then begs other questions. If *Bandolier* can't find answers to obvious questions like those about prescribing and compliance and safety, how do prescribing leads or advisors give sensible advice? The likelihood of unintended consequences is huge.

### Sideways looks

Moreover, what we may be looking at is a massive waste of resources, with a very large proportion of prescribed drugs not being taken (and there is a whole issue of the BMJ given over to the subject in October 2003). Now we don't know how much this is unfilled prescriptions, and how much drugs from filled prescriptions not being taken. But with primary care prescribing costs in England in 2002 being some £7 billion, the scope for untreated illness or waste (or both) is massive.

If it were 10%, that would be £700 million. If it were 30%, that would be £2 billion. Just think of the good that could come from judicious use of those piles of cash.

Someone, somewhere, must have thought of that, so there must, somewhere, be a plan to deal with it. There must be some more, or better evidence. Or is there? So far *Bandolier* has failed to find it. But our readers will know better, so a plea to those of you who know where the evidence is on prescribing waste and how to deal with it, please get in touch.

### KEYBOARD DISCOMFORT

*Bandolier* spends a fair amount of time with its faithful computer. Wonderful things, computers, especially if you have a super whizzo Macintosh and a big screen. But interacting with it is not quite yet the science fiction vision of a polite conversation with a courteous slave with a brain the size of a planet. We interact through a keyboard, using eyes and hands.

The eyes can sometimes get a bit tired, especially looking from paper to screen and back again. That can be helped by a suitable pair of bi-focals. But it's the typing that can be the problem, and the hands, wrists, forearms and neck all protest from time to time. We can minimise that by getting our positions right, and sitting up straight, and a few exercises. But the keyboard, that is not something we often think about.

For some of us the aches can get worse, and develop into real problems, like tendonitis. Is there any evidence out there about the size of the problem (given how many of us use keyboards at work and at home), and whether keyboard design can help if we get into trouble? There's not much, but what there is might be of help.

### Arm and neck pain

Most studies have concentrated on people who use keyboards a lot. An example [1] looked at workers in administrative jobs in Finland who used keyboards (VDUs) for more than four hours a week. It followed 232 who reported little or no neck pain at baseline for a year.

Using the criterion of local or radiating neck pain for at least eight days over the next year, it found that 52 of 180 respondents (34%) fulfilled this criterion. Female sex was about the only major predictor, together with a poor work environment.

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**Table 1: Reports of pain in arms, shoulders and neck in men and women in non-manual occupations in the UK. Statistically significant differences between keyboard users and non-users are shaded**

	Pain in previous week, with adjusted prevalence ratio					
	Women		Men			
	Users	Non-users	Prevalence ratio (95% CI)	Users	Non-users	Prevalence ratio (95% CI)
Neck pain	22.9	18.3	1.3 (1.1 to 1.5)	14.8	13.8	1.1 (0.9 to 1.4)
Shoulder pain	21.2	17.5	1.2 (1.0 to 1.5)	16.4	12.3	1.4 (1.1 to 1.7)
Elbow pain	4.6	4.9	1.0 (0.7 to 1.5)	6.0	5.8	1.2 (0.8 to 1.7)
Wrist or hand pain	15.1	11.0	1.4 (1.1 to 1.7)	10.6	7.9	1.4 (1.0 to 1.8)
Tingling or numbness in upper arm lasting more than 3 minutes	18.1	16.4	1.1 (0.9 to 1.3)	13.3	12.9	1.1 (0.8 to 1.3)

A UK survey [2] of 21,000 randomly selected men and women of working age (16-64) asked questions about use of keyboards for more than four hours per working day, as well as questions on the one week and one year prevalence of pain in neck and upper arms. Responses from 58% had 4,889 responders in non-manual occupations, of whom 1,798 used keyboards for more than four hours a day and 2,901 did not.

One in three non-manual workers reported upper extremity or neck pain during the previous week. Increased wrist and hand pain was associated with frequent keyboard use, as well as neck pain in women and shoulder pain in men (Table 1).

## Keyboard design

The effects of four different keyboard layouts was tested in a randomised, observer blinded study of workers with established tendonitis or carpal tunnel syndrome at the Lawrence Livermore National Laboratories in California [3]. The subjects were all employees, and were eligible to participate if they were full time employees using a computer keyboard for more than four hours a day or 20 hours a month, and whose injuries were recorded in the employer's illness database. All had the diagnosis for less than two years and none had previous hand or wrist surgery or experience of variable geometry keyboards.

Keyboards under test were the workers standard QWERTY keyboard (placebo), and three variable geometry keyboards: an Apple Adjustable keyboard (kb1), a Comfort Keyboard System (kb2), and a Microsoft Natural keyboard (kb3). At the time of randomisation, those randomised to their own keyboard had the keyboard taken away and cleaned, and returned with markings and an assurance that it had been altered.

Various tests on hands, wrists and arms were conducted at baseline and up to 24 weeks of keyboard use, by observers who were blind to the type of keyboard used. The workers themselves made other records about pain and functionality at intervals throughout the study.

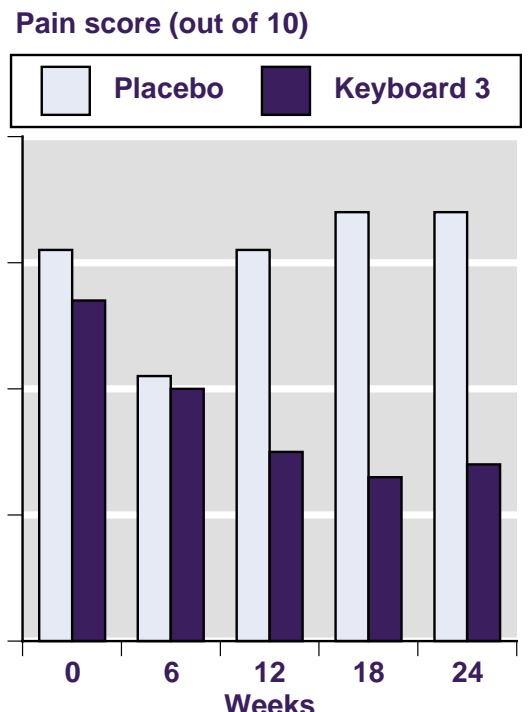
## Keyboard results

Eighty workers were randomised, twenty to each keyboard. Their average age was about 42 years, and about 60% were women. Worker characteristics were well balanced at baseline. No worker gave up using the placebo keyboard, one each gave up on keyboards 1 and 3, but nine stopped working with keyboard 2, five because of mechanical failure. Keyboard 2 was the most complicated.

For all three variable keyboards, more subjects had significant reductions in pain by 50% or more by six months than with the placebo keyboard (Table 2). Keyboard 3 had more responses, and the mean pain scores for this group was significantly lower at 18 and 24 weeks (Figure 1).

While pain scores increased with placebo after six weeks, they tended to fall with other keyboards, but particularly keyboard 3. Keyboard 3 was also the only keyboard where by six months there were significant improvements in func-

**Figure 1: Pain scores over six months**



**Table 2: Responses over six months to placebo and three variable geometry keyboards in workers with established tendonitis or carpal tunnel syndrome**

Change in pain severity	Placebo	Keyboard 1	Keyboard 2	Keyboard 3
Worse	5	3	3	2
Same	10	8	6	7
At least 25% improvement	2	2	3	0
At least 50% improvement	3	7	8	11

tional status scores, particularly for writing, driving, tying shoe laces, performing jobs, using a keyboard and house work. Those workers who thought the variable geometry keyboard was better than their standard keyboard all had a significant reduction in pain.

## Comment

Most of us would accept that spending hours over a hot keyboard can be tiring, and leave us aching. The tendonitis and pain in hands, wrists and forearms that some of us get can be quite severe. It is essential to make sure that position and placing are just right to avoid problems. *Bandolier* finds physiotherapists quite helpful, and some companies have specialists to check out positioning.

There is likely to be a residual burden of people who still have problems, though quite how much is uncertain. The UK study was interesting because it was a population-based examination. It indicated that 15% of British workers use keyboards more than four hours in a working day (and that was in 1998).

While upper extremity pain is common, there is more in people using keyboards a lot. Some of those will have significant pain because of tendonitis or carpal tunnel syndrome. For instance the baseline pain in the randomised trial would be sufficient for entry into acute pain studies. The evidence we have is that persistence with a variable geometry keyboard will make life a lot easier for about half of them.

## References:

- 1 T Korhonen et al. Work related and individual predictors for incident neck pain among office employees working with video display units. *Occupational and Environmental Medicine* 2003 60: 475-482.
- 2 KT Palmer et al. Use of keyboards and symptoms in the neck and arm: evidence from a national survey. *Occupational Medicine* 2001 51: 392-395.
- 3 P Tittiranonda et al. Effects of four computer keyboards in computer users with upper extremity musculoskeletal disorders. *American Journal of Industrial Medicine* 1999 35: 647-661.

## WHERE THERE IS NO EVIDENCE — SEARCH SKILLS

*Bandolier* often finds itself drawn into discussions about how well healthcare professionals are able to find and appraise evidence. A general, if anecdotal, conclusion reached is that:

- ◆ Older professionals have great difficulty in finding evidence, and if presented with it find great difficulty in knowing whether the evidence found is good or bad.
- ◆ Recently qualified professionals whose training included searching and appraisal skills can be very good indeed at both finding and appraising evidence.
- ◆ Recently qualified professionals whose training did not include searching and appraisal skills are no better than their older colleagues in finding and appraising evidence.

The implication is that training in finding and appraising evidence improves professional skills, and that should work through into better use of evidence in practice. What's the evidence for that? A new review [1] tells us that there's not much evidence for the finding part.

## Systematic review

The review from Chorley searched an astonishing eleven different sources, from the Cochrane Library to the Internet. It looked for randomised and other trials of educational interventions for improving on-line searching abilities us-

ing short periods, one to eight hours, of training, compared with another course.

## Results

Three trials were found, all published since 1998, and in all the participants were medical students or junior doctors. Two were randomised, and only one had more than 100 participants.

Two trials, including the largest and possibly the best, found that skills improved after the training course, though benefits were not large, nor were they unambiguous.

## Comment

There is some evidence that training in search skills works, but we really don't know what amount or type of training produces the best results, and in whom. Given that much effort is being expended in critical appraisal and searching skills programmes, we need more and better research on how best to do it.

## Reference:

- 1 A Grag, KM Turtle. Effectiveness of training health professionals in literature search skills using electronic databases – a critical appraisal. *Health Information and Libraries Journal* 2003 20: 33-41.

# STATINS IN OLDER PEOPLE

Another of those frequently asked questions to *Bandolier* is that about the evidence concerning the use of statins in older people. A question that is begged to some extent is what constitutes an older person. One definition is someone a decade or so older than you, but here it is probably someone in their eighth or ninth decades. The answer is that there is evidence from good trials that statins work as well in older people as in younger people.

## Systematic review [1]

This examined five large randomised studies (4S, WOSCOPS, CARE, AFCAPS and LIPID) with just under 31,000 participants, where statin had been compared with placebo, and published before the end of 1998. Statins used were simvastatin and lovastatin on one each, and pravastatin in three, at various doses.

The main outcome for analysis was major coronary events, which included coronary death, nonfatal myocardial infarction, silent infarction, or resuscitated cardiac arrest, as well as unstable angina in one trial. Participants older than 65 years were included in four of the trials.

Risk was reduced by an average of 32% by statins in participants older than 65 years (Table 1), and was similar to the risk reduction in participants younger than 65 years (31%). A similar degree of risk reduction was seen in studies with high and low rates of previous myocardial infarction.

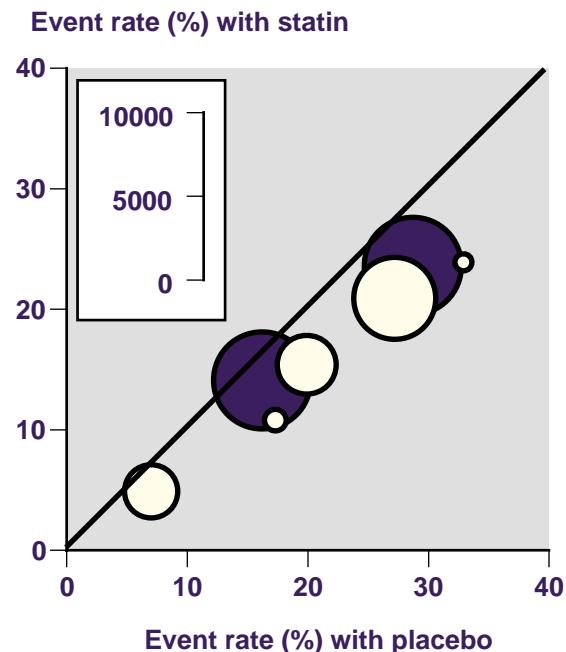
The number of older people needed to be treated with statins for at least five years to prevent one major coronary event was 23 (95% CI 17 to 33).

## Heart Protection Study [2]

HPS randomised 20,536 people aged 40-80 years with coronary disease, occlusive arterial disease or diabetes to 40 mg simvastatin or placebo for five years. The outcome for subgroup analysis by age with about 10,000 people over 65 years was first major coronary event (nonfatal myocardial infarction or coronary mortality).

The results were reported by different age ranges of 65 to 70 years, and over 70 years (Table 1). Risk was reduced with

**Figure 1: Event rates in statin trials in people over 65 years (light symbols) and over 70 years (dark symbols)**



statin by 23% and 18% respectively, and the number needed to treat for five years compared with placebo was 16 and 20 respectively (Table 1).

## PROSPER [3]

This trial randomised 5,800 men and women aged 70 to 82 years with a history of, or risk factors for, vascular disease, to pravastatin 40 mg daily or placebo for a mean of 3.2 years. The primary endpoint was fatal or nonfatal heart attack or stroke.

Risk was reduced by an average of 15% (Table 1). The number of people needed to be treated for three years to prevent an event in one of them was 47 (25 to 358).

## Comment

What we have here is a lot of information about statins in people older than 65 years. Over 25,000 have been included in well done clinical trials, and nearly half of them were over 70 years. There was a consistency of response over all the studies, irrespective of the statin and dose used, the du-

**Table 1: Effects of statins in older people. Note that event rates for the systematic review are approximate, and that somewhat different outcomes were used in different trials**

Study/Review	Age in analysis (years)	Duration (years)	Number in analysis	Event rate (%)		Risk reduction (%, 95%CI)	NNT (95%CI)
				Statin	Placebo		
4S, CARE, AFCAPS, LIPID	65 or older	4.9-6.1	8998	12.0	16.4	32 (26 to 35)	23 (17 to 33)
Heart Protection Study	65 to 70	5	4891	20.9	27.2	23 (15 to 30)	16 (12 to 26)
Heart Protection Study	Over 70	5	5806	23.6	28.7	18 (11 to 25)	20 (14 to 35)
PROSPER	70 to 82	3.2	5804	14.1	16.2	15 (3 to 26)	47 (25 to 358)
Combined data			25499	16.8	21.2	21 (17 to 25)	23 (17 to 29)

ration, or the outcomes reported (Figure 1), and whether these older people were younger or older than 70 years.

Statins are effective in older people, and just as effective as in people aged under 65 or 70 years.

Reading the HPS and PROSPER papers is interesting, because both examine effectiveness by stratification, and show that low levels of HDL cholesterol increase the risk of events. Statins were particularly effective in people with low HDL cholesterol levels.

## References:

- 1 JC LaRosa et al. Effect of statins on risk of coronary disease: a meta-analysis of randomised controlled trials. *JAMA* 1999; 282: 2340-2346.
- 2 Heart protection Study Collaborative Group. MRC/BHF heart protection study of cholesterol lowering with simvastatin in 20,536 individuals: a randomised placebo-controlled trial. *Lancet* 2002; 360: 7-22.
- 3 J Shepherd et al. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. *Lancet* 2002; 360: 1623-1630.

## STEROLS, STANOLS AND CHOLESTEROL

**Bandolier** 64 examined a randomised trial that examined the effects of plant stanols on cholesterol, and found that they were beneficial. But that study was just the one, and with a limited number (100) of subjects. Now we have a systematic review that confirms and extends the results [1].

Plant stanols and sterols have a structure that is very similar to that of cholesterol, and the difference between stanols and sterols is that the former are saturated and the latter are not. Sterols have functions in plants similar to that of cholesterol in animals. Foods enriched with stanols or sterols lower serum cholesterol levels by reducing intestinal absorption of cholesterol.

Stanols and sterols are now found in a variety of margarines and other food products, usually as esters which are hydrolysed in the upper small bowel. They displace cholesterol in absorption processes, though the methods are still speculative.

## Systematic review

Randomised trials that tested foods containing stanols or sterols were found from a previous meta-analysis [2] and review articles, and by questioning experts participating in a specialist workshop.

## Results

There were 41 trials, almost all of which used esterified stanols or sterols. Most used margarine, and most used pla-

cebo margarines or food to ensure double blinding. Mean LDL cholesterol in placebo across all trials was 3.6 mmol/L at 45-54 years and 4.2 mmol/L at 55-64 years.

Stanols or sterols reduced LDL cholesterol by about 10% at all ages (Figure 1). Higher doses gave a larger percentage reduction in LDL cholesterol (Figure 2).

Studies of the use of stanols and sterols in addition to diet or cholesterol lowering agents like statins tended to show an additive effect. A review of safety in human and animal studies showed no adverse effects.

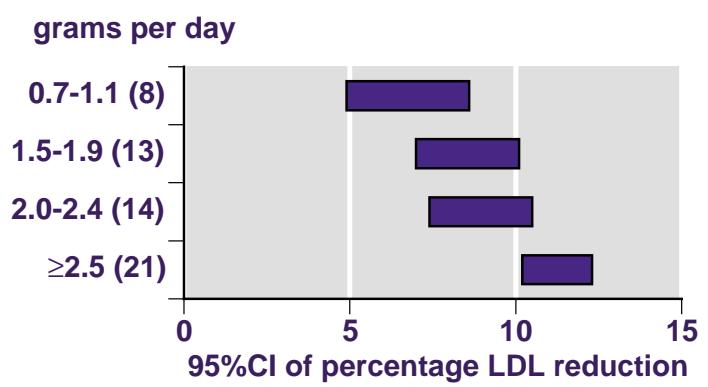
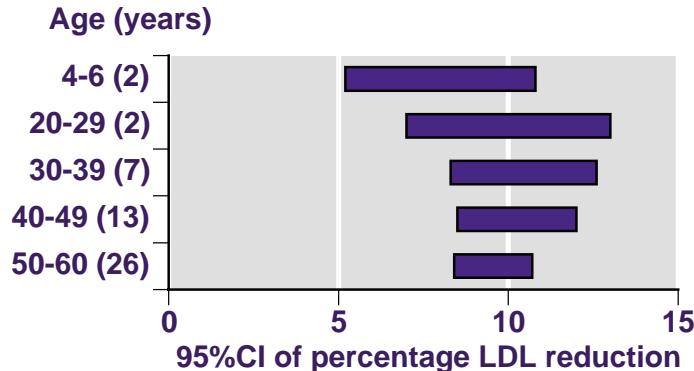
## Comment

The two meta-analyses confirm that stanols and sterols taken at about two grams per day will reduce LDL cholesterol by about 10%, or about 0.3 to 0.5 mmol/L in adults. There is a cost, estimated at about £70 a year because stanols or sterol margarines are more expensive than traditional margarines. But there is also a benefit. The calculation is that this reduction in cholesterol should reduce the risk of heart disease by a quarter [2].

## References:

- 1 MB Katan et al. Efficacy and safety of plant stanols and sterols in the management of blood cholesterol levels. *Mayo Clinic Proceedings* 2003; 78: 965-978.
- 2 M Law. Plant sterol and stanols margarines and health. *BMJ* 2000; 320: 861-864.

**Figure 1: Percentage reduction in LDL cholesterol by plant sterols or stanols according to age of patients (number of trials)**



# WEIGHT LOSS AND BLOOD PRESSURE

**Bandolier** is always on the look out for good evidence about healthy living, and especially about how to avoid having to take antihypertensive medicines. While it is reasonably clear that being overweight may predispose to higher blood pressure, what is the evidence that losing weight reduces blood pressure? And if so, by how much?

Part of the problem in understanding the evidence is the complexity of it all. Are we talking here about normotensive or hypertensive people? Are they on any medicines already? Is weight loss achieved by calorie restriction, exercise, both, or with some added pharmacological help? And what about the length of time taken to lose the weight?

A new and sensible systematic review [1] goes a long way to helping us understand how losing weight helps reduce blood pressure.

## Systematic review

Randomised trials of weight reduction and effects on blood pressure were sought by examining four electronic databases and examination of reference lists from published articles. Those fulfilling inclusion criteria were in English, lasted at least eight weeks, and were of non-pharmacological reduction of body weight.

Where weight and blood pressure were recorded at various points in time during the trial, information was abstracted at the point at which maximal blood pressure reduction was achieved. In the absence of this information, the effect at the end of the study was used.

## Results

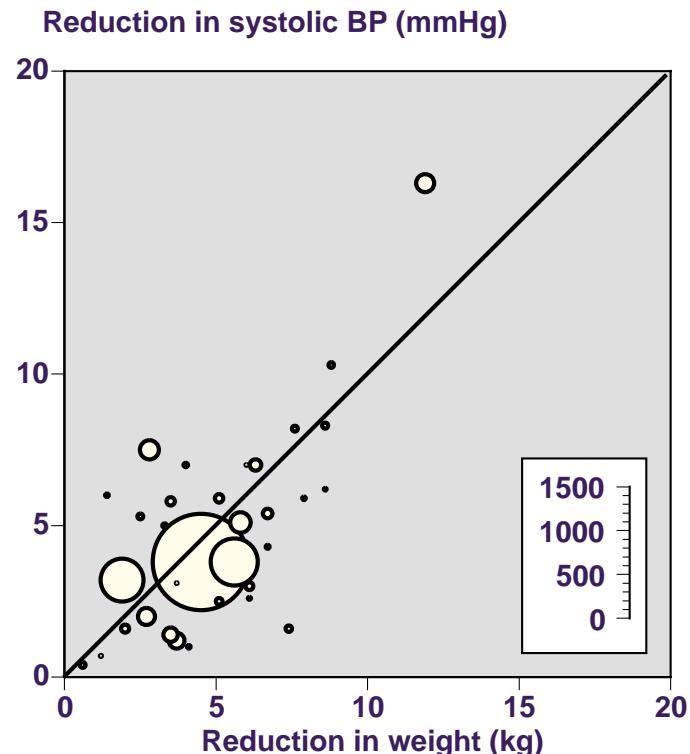
There were 25 eligible trials with 4,874 subjects in trials lasting between eight and 260 weeks, with an average of 67 weeks. The overall mean initial body weight was 88 kg and the overall mean BMI was 31 kg/sq m. Studies most often included both men and women, and the mean ages in the studies varied between 37 and 66 years. About half the populations had initial blood pressures of more than 140/90 mmHg, and about a quarter of the populations were taking antihypertensive medicines. Overall the study withdrawal rate was 4.8%.

The overall mean weight reduction was 5 kg, about a 6% reduction in body weight from baseline. Slightly greater weight loss was found in calorie restricted (7 kg) than exercise alone (3 kg), and combined calorie restriction plus exercise (6 kg).

Changes in systolic and diastolic blood pressure were generally proportional to the amount of weight lost. The relationship for systolic blood pressure is in Figure 1. Overall both systolic and diastolic blood pressure fell by about 1 mmHg for every 1 kg of weight lost.

Various subgroup analyses suggested that this relationship held for younger and older people, for studies with more

**Figure 1: Relationship between weight loss and reduction in systolic blood pressure**



or fewer women, in people who were hypertensive and normotensive, for weight lost by different methods, whatever the initial BMI, and for smaller and larger weight reductions. There were hints that larger reductions in blood pressure for every kg lost might have been seen in Asian populations and people on antihypertensive medicines, but hints they were.

## Comment

What we have here is a common sense review. It used randomised trials of a sensible duration, and found a consistent relationship between weight loss and reductions in systolic and diastolic blood pressure. This is particularly good news for those of a certain age, when weight tends to be a bit on the high side, and blood pressure a bit borderline. It is better to lose a few kilograms than take tablets.

There have been other meta-analyses on weight loss and blood pressure [2, 3, 4], which are worth reading. They confirm a slightly higher response to reduced weight in people on antihypertensive medicines [2], and a general relationship between weight loss and reduced blood pressure [3].

Aerobic exercise may have effects on reducing blood pressure that are additional to those from any weight loss. An analysis of 53 randomised trials [4] in which treatment differences were limited to aerobic physical activity and control demonstrated an overall 4 mmHg reduction in systolic blood pressure and 3 mmHg in diastolic blood pressure when the overall weight change was virtually zero. The reduction tended to be larger with more exercise, and the only caveat was that some of the trials were small, and the small trials had a larger effect.

The clinical bottom line is that, for some people with borderline hypertension, there is a choice. Lose weight and exercise and feel younger and better, or take tablets that might make you feel dreadful. It should be a no-brainer.

#### References:

- 1 JE Neter et al. Influence of weight reduction on blood pressure. A meta-analysis of randomised controlled trials. *Hypertension* 2003 42: e-publication.
- 2 D Ebrahim, GD Smith. Lowering blood pressure: a systematic review of sustained effects of non-pharmacological interventions. *Journal of Public Health Medicine* 1998 20: 441-448.
- 3 CD Mulrow et al. Dieting to reduce body weight for controlling hypertension in adults. *Cochrane Database of Systematic Reviews* 2000 2: CD000484.
- 4 SP Whelton et al. Effects of aerobic exercise on blood pressure: a meta-analysis of randomised, controlled trials. *Annals of Internal Medicine* 2002 136: 493-503.

## MIGRAINE AND MÉNIÈRE'S DISEASE

Text books are generally silent on the question of whether there is any link between migraine and Ménière's disease. Anecdotal accounts of headaches as an additional symptom of a typical Ménière attack go back to the original description in 1861. There is little of note in the literature, and what there is has been criticised.

A new study [1] using strict diagnostic criteria for both conditions in a case-control study is the best evidence yet available for such a link.

### Study

The study population was 114 patients with Ménière's disease seen at a clinic. Diagnosis was based on standard criteria of the American Academy of Otolaryngology of recurrent spontaneous vertigo, with tinnitus or aural fullness, hearing loss, plus exclusion of other causes for the vertigo. Secondary causes like trauma or ear infection were exclusions.

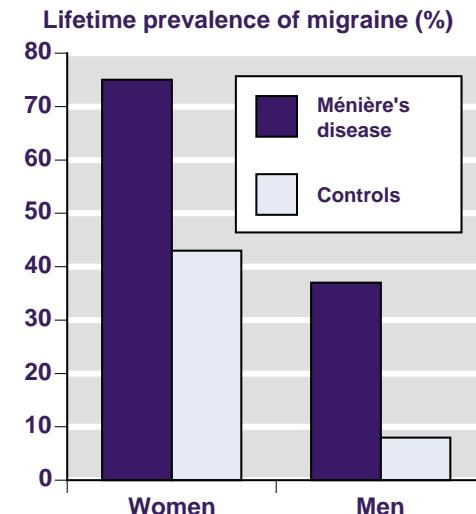
All 114 patients were sent a letter to request their participation. Thirteen patients could not be found, and 78 of the remaining 101 consented to participate. They were 38 men and 40 women aged 29 to 81 years. An age and sex matched control group was selected from patients who had had surgery for orthopaedic problems or trauma.

All participants underwent a semi-structured interview by two neurologists, in which diagnosis of migraine was made using International Headache Society criteria.

### Results

The lifetime prevalence of migraine in patients with Ménière's disease was higher than in controls (Figure 1). Prevalence was considerably higher in women than men, as is well known. The level of statistical significance overall was high ( $p < 0.001$ ) with lifetime prevalence of migraine of

**Figure 1: Relationship between lifetime prevalence of migraine in men and women with Ménière's disease, and controls**



56% in patients with Ménière's disease and 25% in controls. Migrainous headaches during a Ménière attack occurred in 28/78 patients, and photophobia was also common (52/78).

The mean age of onset of Ménière's disease was 46 years on average, some 14 years after the average age of onset of migraine, which was 32 years. Migraine onset preceded onset of Ménière's disease in 33 of 44 patients, was simultaneous in five and later in six.

### Comment

This is an interesting study with a good discussion about the difficulties of dissecting the symptoms and classifications of migraine, vertigo and Ménière's disease. In the absence of other convincing evidence, it does make a strong association between migraine and Ménière's disease more likely. Diagnosis is still going to be problematical, because classical presentation of migraine or Ménière's disease will be relatively uncommon. It makes us think more about people with vertigo and headache, and whether Ménière's disease is a possible diagnosis, where before we would not.

#### Reference:

- 1 A Radtke et al. Migraine and Ménière's disease. Is there a link? *Neurology* 2002 59: 1700-1704.

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# DOSING AND COMPLIANCE?

It is commonly asserted that a medicine that has to be taken once a day is more likely to be taken, and taken correctly, than one that has to be taken in four doses over the same day. **Bandolier** would agree with that from personal experience. While it may seem obvious, we get into difficult territory when someone asks the difficult question about what evidence supports this *obvious* assertion. A review of 20 years ago [1] is the only source **Bandolier** could find.

## Review

The review predates systematic reviews to an extent, but the author tells us that over 100 articles and chapters were examined, as well as library computer searches and examinations of cited references. Studies on patient compliance and dosing of medication were sought.

## Results

There were 57 such studies, 36 regarding compliance with one agent. We know nothing about the study design. A variety of different medicines and conditions were examined in these studies, but 24 examined paediatric, and 32 looked at adult subjects. Definitions of compliance varied, but included pill counts, interviews, and presence of drug in body fluids.

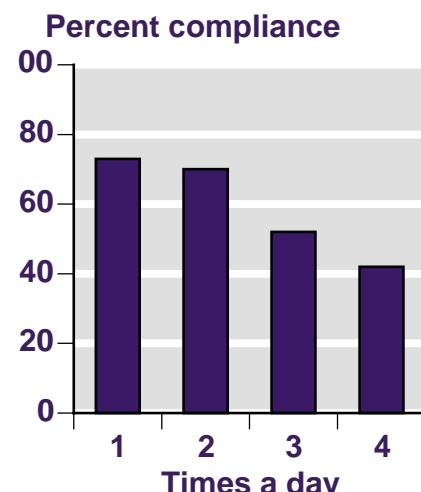
In 26 studies (14 paediatric and 12 adults) there was information relating compliance to dosing schedule, in studies with sizes from 15 to 705 subjects (median 96). The results (Figure 1, Table 1) show a distinct tendency for higher compliance with fewer tablets per day.

## Comment

This is a serious piece of work for a serious and important topic. **Bandolier** was surprised to find nothing more recent (but that may just be a failure to find something obvious). It is full of important observations, particularly about a tendency for elderly patients to make serious errors in dosing.

What we have here is a foundation for a contemporary review of this important topic. It is important for prescribing budgets, as one implication is that a significant proportion of prescribed medicines are not taken. An

**Figure 1: Relationship between daily dosing schedule and average compliance**



average figure of 40% of tablets not being taken might not be far from modern estimates of experienced pharmacists. It is also important for the pharmaceutical companies making once a day medicines, and our response to once a day medicines.

The importance of compliance can be seen with statins. Benner et al [2] used prescription records to study patterns of use in a cohort of 34,501 elderly (65 years or more) patients using statins. They measured the proportion of days covered (PDC) by drug therapy, and the proportion of patients judged to be adherent (taking at least 80% of prescribed drug), partially adherent (20-79% of prescribed drug), or non-adherent (less than 20% of prescribed drug), in each six-month period for a total of 10 years after initiation of therapy.

Most patients lost from the partially adherent group moved into the non-adherent group. Of those who became non-adherent, only 4% had a prescription for another lipid-lowering drug dispensed, and adherence to that drug was also poor. Adverse effects rates are low and could account for only a small amount of the non-adherence. Although this study involved elderly patients from one geographical area (New Jersey), it is in broad agreement with other studies.

Clearly we could do with much more information about what level of compliance, or concordance, or adherence to therapy exists. We also need to know what to do to improve it. We also need good solid data on how much prescribed medicine is wasted.

### References:

- 1 RN Greenberg. Overview of patient compliance with medication dosing: a literature review. Clinical Therapeutics 1984 6: 592-599.
- 2 JS Benner et al. Long-term persistence in use of statin therapy in elderly patients. JAMA 2002 288: 455-461.

**Table 1: Relationship between daily dosing schedule and compliance**

Times a day	Percent taking tablets	
	Range	Mean (SEM)
Once	42-93	73 (6)
Twice	50-94	70 (5)
Three times	18-89	52 (7)
Four times	11-66	42 (5)

**Table 2: Adherence to statin therapy over time**

Months	Adherent	Partially adherent	Non-adherent
3	60	40	0
6	43	29	29
60	26	18	56
120	32	18	50